AMENDMENTS TO THE DRAWINGS

Submitted herewith please find one (1) sheet [Figure 1] of replacement drawings in compliance with 37 C.F.R. § 1.84. The Examiner is respectfully requested to acknowledge receipt of this drawing.

The submitted drawing is intended to replace the drawing previously submitted.

Attachment: Replacement Sheet: One (1)

REMARKS

Status of Claims and Amendment

Claims 1-22 are pending in the application. Claims 3, 4 and 6-22 are withdrawn from consideration. Claims 1, 2 and 5 are rejected. Claims 1 and 5 are objected to. Upon entry of this Amendment, which is respectfully requested, Claim 1 will be amended. Claims 2 and 5 will be canceled.

Claim 1 has been amended to recite "morbid obesity" in place of "obesity". Support for the amendment may be found throughout the specification, and at least at page 2, first paragraph, at page 5, last paragraph, Example 1, and Tables 1-2.

Additionally, Claim 1 has been amended to recite "said alteration is the presence of the following mutation: -243 A>G at nucleotide 2137 of SEQ ID NO: 2". Support for the amendment can be found throughout the specification, and at least at page 2, first paragraph, Example 1, Tables 1-2.

Claim 1 has been further amended to recite a complete gene name, i.e., "glutamate decarboxylase (*gad2*)". Support for the amendment can be found throughout the specification, and at least at page 12, lines 1-3.

Priority

The Office Action acknowledges Applicants' claim for priority to EP 022930853.3 filed December 13, 2002. However, the Office Action asserts that the disclosure of the prior-filed application, EP 022930853.3, fails to provide adequate support or enablement as required by 35 U.S.C. § 112 first paragraph for all of the claimed subject matter. Specifically, the Office Action asserts that the prior foreign application does not provide basis for the protective haplotypes, or SEQ ID NO: 16 or SEQ ID NO: 17, as required by Claim 5.

Claim 5 has been canceled without prejudice. Thus this issue is moot.

Drawings

The drawings are objected to. The Office Action states that while the specification (e.g. p.12 -14) indicates that the -1600 position is a G>A polymorphism and the -2004 position is an A>T polymorphism, Figure 1 indicates '-1.6 G>T' and '-2004 G>A'.

In response, Applicants herewith submit one sheet [Figure 1] of replacement drawings in compliance with 37 C.F.R. § 1.84. The Examiner is respectfully requested to acknowledge receipt of this drawing.

Objection to the Specification

The disclosure is objected to. The Office Action states that Table 1 of the specification (page 14) contains several typographical errors where the letter 'G' is replaced with the number '6', the symbol '%' is replaced by '°io', and the number '8' is replaced with the letter 'g'. Additionally, the Office Action states that Table 2 on page 15 is titled 'fond intake' where the phrase 'food intake' is correct.

In response, Applicants submit herewith a Substitute Specification under 37 C.F.R. § 1.125 (a). In accordance with 37 C.F.R. § 1.125(b), the undersigned states that the Substitute Specification contains no new matter. In accordance with 37 C.F.R. § 1.125(c), a marked up copy of the original specification showing the amendments is also submitted herewith.

Accordingly, entry of the Substitute Specification and withdrawal of this objection is respectfully requested.

Objection to the Specification - Sequence Compliance

The Office Action states that the sequence disclosure of the present application is not in compliance with the requirements of 37 C.F.R §§ 1.821 through 1.825. Specifically, the Office

Action indicates that the present application uses the terms "SEQ ID No" and "SEQ ID N°" instead of a sequence identifier (SEQ ID NO:) in referencing sequences from the sequence listing in the claims and throughout the specification. Additionally, the Office Action states that Claim 5 references "SEQ ID N°16 and 17", where the instant sequence listing contains only 15 sequences.

The substitute specification submitted herewith corrects the sequence identifiers.

With regard to the SEQ ID NOs: 16 and 17 not listed in the sequence listing, Claim 5 reciting the SEQ ID NOs has been canceled. Accordingly, the objection with respect to the sequence listing is rendered moot.

Claim Objections

Claim 1 is objected to over recitation of the gene symbol '*gad2*' rather than reciting a complete gene name. Claim 5 is objected to over the specific recitation of non-elected subject matter in the alternative. The Office Action asserts that Applicants have elected examination of the claims of group I, including Claims 1, 2, and 5, where Claim 5 recites 'the method of one of claim 1 to 4'. The Office Action states that prior to allowance any non-elected subject matter that has not been rejoined will be required to be deleted from the claim.

In response, Claim 1 has been amended to recite a complete gene name, i.e., "glutamate decarboxylase 2 (*gad2*)".

Additionally, Claim 5 has been canceled. Thus, the objection with respect to Claim 5 is rendered moot.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claim 5 is rejected under 35 U.S.C. § 112, Second Paragraph, as allegedly being indefinite. The Office Action states that Claim 5 is unclear since recited SEQ ID NOs: 16 and 17 are not listed in the sequence listing.

Claim 5 has been canceled. Thus, the rejection under 35 U.S.C. § 112, Second Paragraph is rendered moot.

Claim Rejections - 35 U.S.C. § 112, First Paragraph-Enablement

Claims 1, 2, and 5 are rejected under 35 U.S.C. § 112, First Paragraph, as allegedly failing to comply with the enablement requirement.

With respect to the nature of the invention and breadth of the claims, the Examiner states that the instant claims encompass the diagnosis of a predisposition to any type of obesity (e.g., morbid and non-morbid with any BMI) in any population of individuals. Additionally, the Examiner states that the claims encompass the detection of a wide variety of nucleotide content in the diagnosis of obesity predisposition or detecting a protective haplotype. Thus, the Examiner asserts that the claimed invention requires knowledge of a correlative association between nucleotide content and a predisposition for obesity.

As to the direction provided by the specification and working example, the Examiner asserts that the data presented in the instant specification does not provide a consistent statistically significant association between the nucleotide content at the -1.6kb and -2004 positions and morbid obesity in the patient populations that were analyzed. Additionally, the Examiner also contends that the instant specification does not provide any sequence context that indicates the position or content of the requirements for detecting the +61450 or +83897 SNP positions.

Claims 2 and 5 have been canceled. Thus, the rejection is moot as to these claims.

Claim 1 has been amended to recite "morbid obesity". In addition, although Applicants disagree with the Examiner on this rejection, solely to advance prosecution of the present application, Claim 1 has been further amended to recite "wherein said alteration is the presence of the following mutation: -243 A>G at nucleotide 2137 of SEQ ID NO: 2".

With respect to the state of art, level of skill, and level of unpredictability, the Examiner asserts that the instant claims encompass diagnosing a predisposition to any obesity, while the instant specification provides an analysis only of morbidly obese individuals. Accordingly, the Examiner asserts that it is thus unpredictable as to whether or not the asserted associations of the instant specification would be reliably associated with mild forms of obesity.

Applicants assert that the amendment to Claim 1 to recite "morbid obesity" addresses this issue.

With respect to the statistical significance between the SNPs (243G, -1.6kb A, and the -2004 T alleles) and obesity, the Examiner asserts that the instant specification does not provide consistent statistically significant associations, i.e., higher than p=0.05, between the -1.6kb and -2004 alleles and obesity (Table 1). Further, the Examiner asserts that post-filing art (Swarbick et al., 2005 and Hunt et al., 2006) indicates a lack of significant association with obesity in several study populations. Thus, the Examiner asserts that it is highly unpredictable in applying the claimed genetic variations to different groups of subjects or any other individual subject and thus will require undue experimentation to make and use the present invention.

In contrast to the Examiner's assertion, Applicants submit that it is already established in the art that the *GAD2* gene is closely associated with morbid obesity and thus the present invention, which discloses a method of detecting SNPs that affect the expression of the *GAD2* gene, does not require undue experimentation.

Specifically, Applicants note that there is little allelic heterogeneity of the *GAD2* gene among European populations (Ardlie et al. 2002b), and Applicants' family-based data also support this notion. Thus, as mentioned in Boutin et al. (page 368, first column, second paragraph, vol. 1, PLos Biology) the association between *GAD2* SNPs and morbid obesity disclosed in the present specification may not result from a stratification bias. Additionally, Applicants also note that human chromosome 10, where the *GAD2* gene is located, has been known in the art as a susceptibility locus for morbid obesity in four independent ethnic groups (page 1, lines 15-21). Importantly, replication studies in multiple ethnic groups also confirmed the maximum nonparametric linkage peak at D10S197, which is located in the intron 7 of *GAD2* gene encoding a glutamate decarboxylase enzyme (Price et al., 2001, Saar et al. 2003, Boutin et al., 2003). Glutamate decarboxylase converts glutamate into γ-aminobutyric acid (GABA), a neurotransmitter which interacts with NPY in the paraventricular nucleus to stimulate food intake (Pu et al. 1999). Thus, Applicants submit that circumstantial evidence has already established a critical role for the *GAD2* gene in regulating food intake behavior and obesity. Indeed, knocking down the *GAD2* gene in rat ventromedial hypothalamus using antisense technology, which reduces the content of GABA by 50%, decreases the food intake and stimulates locomotor activity, which directly affects obesity (Bannai et al., 1998). Therefore, the question that remains in the art is what changes in the *GAD2* gene or in its regulatory region are responsible for obesity. In this connection, the present invention provides strong evidence that the SNP (-243 A>G) located in the 5' promoter region of *GAD2* gene affects the expression of the gene (Figure 1). For example, the instant specification discloses that the mutation at -243A>G significantly increases the expression of *GAD2* gene as demonstrated by a luciferase reporter assay (Figure 3).

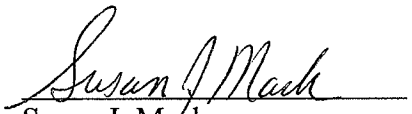
Nonetheless, Applicants assert that the amendment to Claim 1 to recite "said alteration is the presence of the following mutation: -243 A>G at nucleotide 2137 of SEQ ID NO: 2" overcomes this aspect of the rejection.

Accordingly, the Examiner is requested, respectfully, to reconsider and remove this rejection.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



Susan J. Mack
Registration No. 30,951

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: February 23, 2009